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REVIEW ARTICLE

Genetic landscape of epilepsies in Kingdom of Saudi Arabia: a brief review

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ABSTRACT

Epilepsy is a common chronic neurological problem with a prevalence rate of 6.5 per 1,000 in Saudi Arabia. In the field of epilepsy genetics, the rapid pace of gene discovery has resulted in exciting advances. Clinical testing using comprehensive gene panels, exomes, or genomes is becoming more widely available, resulting in a higher diagnostic yield in early-onset epilepsies and enabling precision medicine approaches. The genetic screening techniques include comparative genomic hybridization, single-gene testing, chromosomal analysis, epilepsy panel testing, whole-exome sequencing (WES), and whole-genome sequencing. It is essential to know the classification of genetic epilepsies to choose the appropriate genetic test for its differential diagnosis. Although there have been various classifications reported by different groups, the most acceptable one is to classify them based on type of epilepsy, type of gene involvement, and age of onset of epilepsy. The diagnosis of genetic epilepsies helps the treating physician determine the prognosis, select the appropriate medications, and avoid certain medications that may exacerbate epilepsy. In Saudi Arabia, recently genetic tests have been made available in many centers. Various research groups have discovered and reported a wide range of genes, especially pediatric neurologists, geneticists, and neurogenetics across the Kingdom. The availability of WES due to its cost-effective nature is another reason for the advancement in epilepsy screening in the Kingdom. The present review aims to discuss the genetic testing of epilepsy, classification of genetic epilepsies, epilepsy genetics in Saudi Arabia, and the future of epilepsy genetics in Saudi Arabia.

Keywords: Genetic epilepsy, epilepsy classification, genomic hybridization microarray, Saudi Ar abia, next-generation sequencing, BFNIE, BFIE.

Introduction

Over the last 50 years, genetics showed significant advancement contributing to the improved diagnosis and management of various diseases (1,2). Genetics is an important field for all subspecialties in medicine, including pediatric neurology. In the past, genetic testing was limited to particular diseases like those with dysmorphic features or specific family history or specific genetic background, or specific clinical syndrome. The advancement of genetics became an essential tool in pediatric neurology and epilepsy (3) in terms of the rate and accuracy of the diagnosis. Furthermore, it helps the physician be confident of the diagnosis based on clinical findings, helps inpatient management, and provides a clear idea about the prognosis for the parents and the physician. Epilepsy is a common chronic neurological problem with a prevalence rate of 6.54 per 1,000 in Saudi Arabia (4,5). It is diagnosed when two unprovoked events occur within 24 hours or with the presence of one unprovoked event with a high risk of recurrence or epilepsy syndrome. When a diagnosis of epilepsy is performed, the physician tries to find its etiology. However, around 60%-70% of epilepsy are idiopathic, meaning no organic or structural causes are found (6). However, with the advances in genetics, the percentage of idiopathic epilepsies decreased, and genetic causes of epilepsy are being identified (7-10).

When Would the Physician Suspect Epilepsies with a Genetic Background?

Performing genetic testing is not a routine practice in any case of epilepsy. However, a physician would think only when the following criteria are fulfilled:

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normal development, absence of structural or focal lesions in neuroimaging, family history of epilepsy, presence of phenotype, which indicates an epilepsy syndrome, presence of epilepsy in young age groups like infants, presence of seizure when just awakened, electroencephalogram (EEG) showing 3 Hz spike and wave discharges and presence of dysmorphic features with epilepsy. Then, after having the clinical, biochemical, neuroimaging, and electrophysiological examinations, the physician, might choose the appropriate genetic testing (7,11).

Type of Genetic Tests Available for Epilepsy

Comparative genomic hybridization (CGH) microarray

CGH is the first type of genetic test performed for patients suggestive of genetic etiology for epilepsy. Its yield is variable and reaches approximately 25% when there is generalized genetic epilepsy (GGE). The output is estimated to be higher when there is a concomitant developmental delay or intellectual disability. However, generally, a definitive diagnosis in all cases of epilepsy using CGH is less than 5% (2,6,12).

Single gene testing

Single gene testing is suggested for patients presented with phenotype and EEG, which support a specific epilepsy syndrome. In addition, single-gene testing is cost-effective and less time-consuming compared to other tests available (9,10,13).

Chromosomal analysis

Chromosomal analysis is suggested for patients with dysmorphic features, developmental delay or cognitive impairment, and refractory epilepsy, especially when the CGH microarray results are normal (1,6,9,14). In addition, on certain occasions, specific EEG findings may suggest a chromosomal disorder like ring chromosome 20 (15).

Epilepsy panel testing

Epilepsy panel testing analyses the most common genes causing epilepsy to utilize next-generation sequencing (NGS) technology. A wide range of epilepsy panels is available, ranging from larger panels with 500 genes to smaller panels with 20-30 genes. Also, there are epilepsy panels that are specific for those with the age of onset of seizure-like infantile age, presence of encephalopathy, and specific types of epilepsy like an infantile spasm. (1,6,15,16). The yield of this test is around 15%-25% (9).

Whole-exome sequencing (WES) and whole-genome sequencing (WGS)

WES and WGS initially introduced were costly. However, it became cost-effective with time, making it more available for pediatric neurologists and geneticists to order it for their patients. This test utilizes NGS to sequence all of the exons or proteins coding regions in DNA. However, besides the high cost, other limitations include identifying unrelated variants for epilepsy, lack of availability in medical centers, and time-consuming sample outsourcing at medical centers without NGS facilities (1,6,17-20). This testing yield is ranged between 20%-40%, but it may be higher when a trio-based analysis is considered (2,21-24).

Classification of Genetic Epilepsies

Genetic epilepsies are classified based on three parameters: type of epilepsy, type of gene involved, and age of epilepsy onset.

Type of epilepsy

It is essential to verify whether the patient has a generalized or focal seizure regarding the clinical presentation or EEG findings. Each category may suggest specific genetic epilepsy syndromes. Hence, it could restrict the number of genetic disorders causing epilepsy, especially when normal development, cognitive function and neuroimaging. The genetic disorder causing generalized epilepsy is referred to as GGE. The GGE further includes juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), and juvenile absence epilepsy (JAE), and each type has its causative gene (9) (Table 1). focal genetic epilepsy (FGE) syndrome refers to the genetic disorder causing focal or partial seizures where the epileptic discharges arise from specific localization in the brain: some of these disorders occur from either the frontal or temporal lobe. Nocturnal frontal lobe epilepsy (NFLE), or sleep-related hyper motor epilepsy (SHE), is an autosomal dominant disorder that arises from the frontal lobe and exclusively occurs during sleep, presenting with focal seizure with or without secondarily generalization (9). Several genes, including *CHRNA4*, *CHRNA2*, *CHRNB2*, *PRIMA1*, and *KCTN1*, cause this syndrome. Familial temporal lobe epilepsy (FTLE) arises from the temporal lobe and may be associated with mesial temporal lobe sclerosis (25). However, most cases of temporal lobe epilepsy are sporadic. The recognized genes associated with FTLE are *SCN1A*, *SCN1B*, and LGI1. Tuberous sclerosis is another FGE syndromes with a genetic background related to the mammalian target of rapamycin pathway and has specific genes *TSC1* and *TSC2*. Vascular anomalies of the brain can cause focal epilepsy. Porencephaly, which occurs as intrauterine cerebral ischemia and is mainly presented with focal seizure. mutations cause it is the COL4A1 and COL4A2

***Table 1**. Types of epilepsy.*

Infantile	**Gene**
BFNE	*KCNQ2, KCNQ3*
BFNIE	*SCN2A*
BFIE	*PRRT2, SCN2A, KCNQ2, KCNQ3*
Childhood	**Gene**
CAE	*SCLC2A1*
JAE	*CACNB4, CLCN2*
JME	*GABRA1, EFHC1, CACNB4, CLCN2*

genes. Also, Sturge-Weber syndrome is considered one of the brain's vascular anomalies that cause focal seizures and has been reported to be associated with GNAQ gene mutation (somatic mutation) (9). Another type of FGE syndromes is associated with glutamate, known as an excitatory neurotransmitter. Landau-Kleffner syndrome(LKS) is caused BY mutations in the GRIN2A although few other genes are suggested as causative factors, including RELN, BSN, EPHB2, and NID2 (26). Generally, the yield of genetic testing is higher in GGE than FGE syndrome (9,10).

Types of Genetic Background

Mendelian disorders

Mendelian disorders are also termed AS single-gene disorders. The mutation in a single gene causes a change in a single primary locus that decreases gene expression or complete loss of function.

Chromosomal disorder

Chromosomal disorders result from autosomal chromosomes, which result in a change in the structure, number, or deletion of the chromosomes. Examples are ring chromosome 20, Miller dicker syndrome, and Angelman syndrome.

Mitochondrial disorder

It involves mutation of mitochondrial DNA, which is inherited from the mother.

Complex disorders

It is also known as non-Mendelian or multifactorial. Usually, it involves a couple of genes, which are influenced or triggered by environmental factors. Examples are JME and childhood epilepsy.

Epigenetic disorder

These disorders involve a change in the activity of the gene rather than its structure.

Age of onset of epilepsy

One way of classifying genetic epilepsy is the age of the patient at which epilepsy occurs, thus, restricting the differential diagnosis of the genetic epilepsies. These include infantile genetic epilepsies, where epilepsy began in the first year of life, such as benign familial neonatal epilepsy (BFNE), benign familial neonatal-infantile epilepsy (BFNIE), and benign familial infantile epilepsy (BFIE). Childhood genetic epilepsies, which occur after the first year of life, include JME, CAE, and JAE (Table 2) (7,14).

Do genetic Tests Affect Management?

The genetic test in epilepsy is essential mainly for diagnosis and prognosis. However, these tests may change the management of epilepsy either by avoiding certain drugs that may exacerbate the seizures or by selecting the first line of drugs that are effective in such type of genetic epilepsy. In addition, on occasions, the genetic test may be informative to treat the primary etiology causing the seizure and helps in curing not only the seizure attacks but also the development and cognitive function of the patient (1,8).

Epilepsy Genetics in the Kingdom of Saudi Arabia (KSA)

Epilepsy genetics in KSA showed significant advances and improvement due to the availability of advanced genetic tests across the Kingdom. Furthermore, an increased number of geneticists, especially neurogenetics and genetic counseling departments, help pediatric neurologists to diagnose genetic epilepsies and improve management.

In a recent study from KSA using NGS, 65 patients were investigated having hallmark features of epilepsy, of which 21.5% were tested positive, 24% were inconclusive cases, and 53% had a negative impact. CGH has been performed for 30 NGS negative cases, and 4 cases with pathogenic variants were identified. The overall diagnostic yield of exome/genome sequencing was estimated at 23% (27). Similarly, Nashabat et al. (28) reported a case series of early infantile epileptic encephalopathies (EIEE). They reported the most extensive case series in the region (72 cases) with confirmed molecular testing and detailed clinical phenotyping and identified 50 variants, 26 of which were novel, causing 26 different types of EIEE.

Table 2. *Age of onset of epilepsy.*

GGE	**Gene**
CAE	*SCLC2A1*
JAE	*CACNB4, CLCN2*
JME	*GABRA1, EFHC1, CACNB4, CLCN2*
Generalized Epilepsy with Febrile Seizure Plus	*SCN1A, SCN2A, SCN1B, GABRD, GABRG2*
FGE	**Gene**
NFLE (SHE)	*CHRNA4, CHRNA2, CHRNB2, PRIMA1, KCTN1*
FTLE	*SCN1A, SCN1B, LGI1*
LKS (acquired epileptic aphasia)	*GRIN2A, RELN, BSN, EPHB2, NID2*
FE due to vascular anomalies (e.g., porencephaly)	*COL4A1, COL4A2*
Sturge Weber Syndrome	*GNAQ*
Tuberous sclerosis	*TSC1, TSC2*

Furthermore, mutations in the *NECAP1* gene in a Saudi family were discovered to be associated with early-onset epileptic encephalopathy (29). In addition, few other research groups identified several genes causing epilepsy in Saudi patients. Alsaif shahad et al. (30) described biallelic *SCN2A* gene mutation causing early infantile epileptic encephalopathy. Algahtani et al. (31) identified a novel intronic variant in the *SLC2A1* gene in a Saudi patient with myoclonic epilepsy. Naseer et al. (32) described a novel homozygous mutation in the SZT2 gene in Saudi families with developmental delay, macrocephaly, and epilepsy. The recent studies in the Kingdom reporting novel and pre-identified genes for epilepsy reflect the physician's understanding and the advancement of genetic testing in the Kingdom.

Future Perspective

The advance of genetic testing will help and improve the management of patients with epilepsy. Furthermore, it would also contribute to a better understanding of epilepsy (development of seizures) and the pathophysiology of the disease itself. Therefore, the pediatric neurologist and epileptologist should know that these advances will help early management and epilepsy and avoid a delay in treatment or intractability.

Summary and Conclusion

Genetic testing is essential for pediatric neurologists and epileptologists for epilepsy diagnosis, prognosis, and treatment. The advancement in the genetic field would help discover more epilepsy syndromes and genetic epilepsies, which could improve patient care. The diagnostic yield of genetic tests increases when combined with a very dedicated clinical assessment. A collaboration between the pediatric epileptologist and the geneticist is essential, especially in complicated or unclear results.

List of Abbreviations

BFIE	Benign familial infantile epilepsy
BFNE	Benign familial neonatal epilepsy
BFNIE	Benign familial neonatal-infantile epilepsy
CAE	Childhood absence epilepsy
FGE	Focal genetic epilepsy
FTLE	Familial temporal lobe epilepsy
GGE	Generalized genetic epilepsy
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
NFLE	Nocturnal frontal lobe epilepsy
SHE	Sleep-related hyper- motor epilepsy

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